Institution: Imperial College London

Unit of Assessment: 04 Psychology, Psychiatry and Neuroscience

Title of case study: Stars in their eyes: gene therapy for degenerative eye disease

Period when the underpinning research was undertaken: 2000 - 2015

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Miguel Seabra	Chair in Molecular Biology	1997 - 2015
Tanya Tolmachova	Research Fellow	1997 - 2017
Oleg Tolmachov	Research Associate	2013 - 2014

Period when the claimed impact occurred: 2013 - 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Professor Seabra's early research funded by the Choroideremia Research Foundation and Fight for Sight led to discovery of the biochemical basis for choroideremia and the subsequent development of tests for its specific diagnosis. Seabra along with Robert MacLaren and Matt During then developed a first gene therapy vector (NSR-REP1), leading to the first treatment trial and evidence for sustained arrest or significant improvement in vision for some of the patients treated. A successful spin-out company, Nightstar Therapeutics was created on these foundations, with NSR-REP1 as its lead programme. Nightstar gained significant investment, went public in 2017 and was subsequently acquired by Biogen in 2019 for approximately $800,000,000.

2. Underpinning research (indicative maximum 500 words)

Choroideremia is a rare disease of the eye affecting approximately 1 in 50,000 (predominantly males), causing progressive vision loss beginning usually in late childhood. The first signs are usually related to a loss of night vision (night blindness), followed by a reduction in the field of vision and a growing inability to discern details, depth and colour perception. This eventually leads to blindness in adulthood by the fourth decade.

The disease has long been without any cure. Choroideremia is caused by faults in the *CHM* gene. Professor Miguel Seabra, at Imperial College London, defined the biochemical basis for the disease for the first time, showing that a disease-associated *CHM* gene defect causes a certain protein - known as REP-1 - not to be produced in most cases. Lack of this protein causes pigment cells in the retina of the eye to deteriorate, leading to damage to the eye tissue. *CHM* gene defects are inherited on the X-chromosome, so that males are more likely to develop the condition in affected families, but females can pass the faulty *CHM* gene onto their children.

An important hurdle to developing a treatment was to learn where the disease starts in the retina. This could only be done by creating mouse models that could allow the course of the disease to be followed. Seabra achieved this using a newly developed method which allowed the deletion of the *CHM* gene in distinct layers of the retina of a mouse (called conditional mouse knock-outs) (1). Study of these models demonstrated that the retinal pigment epithelium (RPE) and photoreceptors degenerate independently. Importantly, he discovered that the greatest pathological effects occurred with expression of mutant protein in the retinal pigment epithelium layer, identifying it as the most important target layer for therapeutic correction (2).

Seabra and his colleagues then developed a serotype 2 adeno-associated viral vector AAV2/2-CBA-REP1 for therapeutic delivery of the human transgene and showed that sub-retinal injections of the vector to reach the retinal pigment layer improved retinal function in the mouse model (3).

A pioneering Phase 1/2 clinical trial to assess the effect of retinal gene therapy in collaboration with Prof Robert MacLaren at Oxford and Matthew During in Ohio was undertaken based on results in Seabra's experimental system, defining the specific retinal pigment layer therapeutic target and the potential safety and efficacy of the vector (4). The results of the trial in 2014 indicated that after 6 months patients showed improvement in their vision in dim light and two of the six patients were able to read more lines on an eye chart. On the basis of this, the vectors and its uses were patented with Seabra, MacLaren and During as inventors.

3. References to the research (indicative maximum of six references)

(1) Tolmachova, T., Anders, R., Abrink, M., Bugeon, L., Dallman, M.J., Futter, C.E., Ramalho, J.S., Tonagel, F., Tanimoto, N., Seeliger, M.W., Huxley, C., Seabra, M.C. (2006). Independent degeneration of photoreceptors and retinal pigment epithelium in conditional knockout mouse models of choroideremia. *Journal of Clinical Investigation*; 116(2): 386-94. DOI.

(2) Tolmachova, T., Wavre-Shapton, S.T., Barnard, A.R., MacLaren, R.E., Futter, C.E., Seabra, M.C. (2010). Retinal pigment epithelium defects accelerate photoreceptor degeneration in cell type-specific knockout mouse models of choroideremia. *Investigative Ophthalmology & Vision Science*; 51(10): 4913-20. DOI.

(3) Tolmachova, T., Tolmachov, O.E., Barnard, A.R., de Silva, S.R., Lipinski, D.M., Walker, N.J., Maclaren, R.E., Seabra, M.C. (2013). Functional expression of Rab escort protein 1 following AAV2-mediated gene delivery in the retina of choroideremia mice and human cells ex vivo. *Journal of Molecular Medicine (Berl)*; 91(7): 825-37. DOI.

(4) MacLaren, R.E., Groppe, M., Barnard, A.R., Cottriall, C.L., Tolmachova, T., Seymour, L., Reed Clark, K., During, M.J., Cremers, F.P.M., Black, G.C.M., Lotery, A.J., Downes, S.M., Webster, A.R., & Seabra, M.C. (2014). Retinal gene therapy in patients with choroideremia: inital findings from a phase 1/2 clinical trial. *Lancet*; 383: 1129-37. DOI.

Key funding:
Choroideremia Research Foundation, 2002 - 2005, £21,220
Choroideremia Research Foundation, 2005 - 2006, £27,312
Choroideremia Research Foundation, 2006 - 2008, £87,314
Choroideremia Research Foundation, 2008 - 2009, £30,079
Choroideremia Research Foundation, 2009 - 2011, £104,320
Fight for Sight, 2007 – 2011, £150,000
Fight for Sight, 2011 – 2016, £182,752

4. Details of the impact (indicative maximum 750 words)

Choroideremia is a rare degenerative retinal disease which presents as night blindness and progressive visual field constriction from late childhood, leading to blindness in men typically in the fourth decade. Choroideremia presents in a milder form in women. It affects approximately 1 in 50,000 people. Neither specific diagnostics nor any treatment for the disease were available before the Imperial College research.

The preclinical work from Prof Miguel Seabra in defining the underlying biochemical mechanisms of choroideremia has had a major impact on its diagnosis and subsequent treatment. Diagnosis of the disease, which can be strikingly variable even within the same family, was based previously only on characteristic fundus findings and family history. Diagnoses in suspected cases can now be confirmed by direct genetic testing or through immunoblot analysis with anti-REP-1 antibody to

differentiate it from related disorders, which could have both therapeutic and prognostic relevance [**A**].

Seabra developed the first mouse models for the disease and discovered the cells in the retina responsible for initiating the disease. With MacLaren, he developed a therapeutic adeno-associated virus serotype 2 (AAV2) treatment vector, AAV-REP1, and showed its potential efficacy and safety with sub-retinal injection in the mouse. This led to a first-in-man clinical trial that provided first evidence for clinical benefits. Based on this, a successful patent (US20140107185A1) for invention of gene therapy of choroideremia based on retinal gene therapy using the human *CHM* transgene and methods of preventing or treating this disease using the vector was filed with MacLaren and During [**B**].

With completion of the first trial and follow up of patients, Seabra, MacLaren and their colleagues were able to show the gene therapy had a profound impact on treatment for vision in some of those who received it. Sustained visual acuity gains were seen over a period of several years in end-stage eyes, in which rapid visual acuity loss would ordinarily be expected, with several patients experiencing gains of three lines or more, an improvement widely accepted to be clinically significant [**C**]. Professor Robert MacLaren, the ophthalmologist who led the trial, said:

"*The early results of vision improvement we saw have been sustained for as long as we have been following up these patients and in several the gene therapy injection was over 5 years ago. The trial has made a big difference to their lives*." [**D**].

The trial also led to surgical innovations in the development of an automated injection system directed by intraoperative retinal scanning using optical coherence tomography, that informed subsequent trials and whose impact has been to minimise surgical adverse events with the sub-retinal delivery of genetic therapies [**C**].

The research has had substantial economic impact, in addition to that clinically. In 2014. the investigators formed a spinout company in conjunction with Isis Innovations in Oxford, NightstaRX Limited, (subsequently renamed Nightstar Therapeutics) in which Imperial College held an equity share. Treatment of choroideremia was the lead programme for Nightstar, which received series A, B, and C funding from Syncona Limited and other investors [**E**].

The leading gene therapy programme, known as NSR-REP1, has been prosecuted in phase 1 and 2 trials, and the company started an international phase 3 study, the 'STAR' trial in 2018. Nightstar Therapeutics raised $75,000,000 through a NASDAQ IPO in 2017 [**F**] to fund the phase 3 trial and its other programmes. Investment subsequently grew to $500,000,000 [**G**]. In July 2019, Biogen acquired Nightstar for over $800,000,000 to boost its clinical ophthalmology assets, where gene therapy for choroideremia (NSR-REP1) was noted as the lead asset being purchased [**H**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Zinkernagel, M.S., MacLaren, R.E. (2015). Recent advances and future prospects in choroideremia. *Clinical Ophthalmology;* 9: 2195-2200. DOI.

[**B**] https://patents.justia.com/patent/20140107185#history (Archived here).

[**C**] Xue, K., Jolly, J.K., Barnard, A.R., Rudenko, A., Salvetti, A.P., Patrício, M.I., Edwards, T.L., Groppe, M., Orlans, H.O., Tolmachova, T., Black, G.C., Webster, A.R., Lotery, A.J., Holder, G.E., Downes, S.M., Seabra, M.C., MacLaren, R.E. (2018). Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia. *Nature Medicine*; 24(10): 1507-1512. DOI.

[**D**] https://www.fightforsight.org.uk/our-research/inherited-eye-diseases/world-first-gene-therapy-that-is-already-restoring-

sight/#:~:text=Professor%20Robert%20MacLaren%20the%20ophthalmologist,big%20difference%20to%20their%20lives.%E2%80%9D (Archived here)

[**E**] https://www.curechm.org/2017/10/nightstar-therapeutics-raises-75-million-in-ipo-to-fund-pivotal-phase-3-gene-therapy-study/ (Archived here).

[**F**] https://www.synconaltd.com/media/1379/nightstar-timeline-2019-08-15.pdf (Archived here).

[**G**] https://www.clustermarket.com/articles/nightstar-therapeutics (Archived here).

[**H**] http://investors.biogen.com/news-releases/news-release-details/biogen-completes-acquisition-nightstar-therapeutics (Archived here).